

REMARKS

Claims 1, 38, 40, and 58 are pending in this patent application. No claims have been amended, canceled, or added, herein. Applicants respectfully request reconsideration of the rejections of record in view of the following remarks.

Alleged Double Patenting

Claims 1, 38, and 40 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1, 5, 9, 11, 79, and 80 of copending U.S. patent application number 10/700,689. Applicants request deferral of this rejection pending the identification of allowable subject matter in the present application, as the rejection can likely be readily resolved, depending upon the subject matter ultimately allowed, through the filing of a suitable terminal disclaimer.

Alleged Obviousness

A. Claims 1, 38, 40, and 58 have been rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by published U.S. patent application number 2003/143732 (“the Fosnaugh application”) in view of published U.S. patent application number 2003/0166282 (“the Brown application”). Applicants respectfully request reconsideration and withdrawal of the rejection because the Fosnaugh and Brown applications fail to teach or suggest the subject matter recited in the claims, and, hence, fail to render the claimed subject matter obvious.

To establish *prima facie* obviousness, the Patent Office must demonstrate that the cited prior art reference or combination of references teaches or suggests all the limitations of the claims. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974); *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). The Patent Office must also identify “a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.” *KSR Int’l Co. v. Teleflex*, 127 S.Ct. 1727, 1741. In other words, the Office must identify “an apparent reason to combine the known elements *in the fashion claimed by the patent at issue*. To facilitate review, this analysis should

be made explicit.” *KSR Int’l. Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (emphasis added)(citing *In re Kahn*, 441, F.3d 977, 988 (Fed. Cir. 2006).

The claims recite compositions comprising first and second chemically synthesized oligomeric compounds in which the first oligomeric compound comprises at least one 2'-fluoro modified nucleoside and the second oligomeric compound comprises at least one nucleoside comprising an inosine base. At least one of the nucleosides comprising an inosine base is the 3'-terminal hybridizing nucleoside of the second oligomeric compound, and the 5'-terminal hybridizing nucleoside of the second oligomeric compound comprises a guanine or cytosine base.

The Fosnaugh application fails to teach or suggest first and second oligomeric compounds bearing the particular pattern of chemical modifications claimed. Instead, the Fosnaugh application merely provides generalized teachings regarding chemical modification of RNA. The Fosnaugh application provides a broad listing of possible chemical modifications for RNA and states that such modifications can be incorporated into siRNA molecules.¹ The described chemical modifications could be incorporated into oligomeric compounds in a virtually limitless number of possible patterns and combinations. The Fosnaugh application does not provide any guidance or detail regarding the particular types of chemical modifications, the number of chemical modifications, and the positioning of chemical modifications that should be present in an siRNA molecule to impart beneficial properties to the molecule.

Significantly, all of the oligonucleotides described in the Fosnaugh application possess the same modification for each particular type of nucleobase throughout the oligonucleotide. For example, all of the adenosines of a particular oligonucleotide have the same modification throughout the oligonucleotide, as do all of the cytosines, etc. Consequently, the pattern of modifications depends entirely on the base sequence of the particular oligonucleotide. This sequence-dependent substitution scheme teaches by implication that the pattern or position of modifications does not matter, but, rather, what matters is the base sequence of the oligonucleotide or the mere presence or number of modifications. The present claims, to the

¹ Paragraph 39.

contrary, identify particular positions or patterns of modification, independent of the base sequence of the recited oligomeric compounds. Thus, not only does the Fosnaugh application fail to teach the specifically claimed motif of chemical modification, it actually teaches away from the core concept of sequence-independent patterns of modification.

The Brown application describes double-stranded RNAs having duplex structures of reduced stability that are said to be useful as small interfering RNAs (siRNAs).² The application indicates that a variety of techniques may be used to reduce the stability of the siRNA duplexes, including introducing nucleotide analogs into the duplexes, and the application provides a “non-limiting list of possible modifications to be made to the siRNA.”³ Such modifications include introducing one or more phosphorothioate linkages into the siRNA molecules, substituting inosine bases for guanine bases at one or more positions in the siRNA duplexes, substituting 4-thiouridine bases for one or more uracil bases, introducing 4-ethyl cytosine at one or more positions in the siRNA duplexes, substituting “an appropriate number” of nucleotides in the siRNA molecules with 3-nitropyrrole and/or 5-nitroindole nucleotides, introducing one or more abasic sites in the sense strand of the siRNA molecules, and introducing one or more mismatches in the siRNA molecules.⁴

Significantly, nothing in the Brown application suggests to those skilled in the art that incorporation of an inosine base would be any more advantageous or desirable than incorporation of any of the other chemical modifications described in the application. Moreover, the Brown application provides no guidance regarding the position or the strand at which the described chemical modifications should be introduced, much less that such modifications should be incorporated at the 3'-terminal hybridizing nucleosides of the sense strand of the siRNA duplexes. The application thus cannot render obvious an inosine base at 3'-terminal hybridizing nucleosides of the sense strand, as claimed. In addition, the Brown application fails to describe introducing at least one 2'-fluoro modified nucleoside into the antisense strand of the siRNA molecules. The Brown application thus fails to describe or suggest the claimed first and

² Paragraphs 18 and 29.

³ Paragraphs 31 to 38.

⁴ *Id.*

second oligomeric compounds in which the first oligomeric compound comprises at least one 2'-fluoro modified nucleoside and the second oligomeric compound comprises an inosine base at the 3'-terminal hybridizing nucleoside.

The appropriate design for chemically modified siRNA molecules having enhanced properties relative to unmodified compounds would have been unpredictable to those of ordinary skill in the art at the time of applicants' invention in view of the cited art. Such artisans would have had no reason to select the particular pattern of chemical modifications presently claimed from the enormous number of possible patterns of chemical modifications taught by the Fosnaugh and Brown applications. In fact, the Fosnaugh application actually teaches away from the claimed pattern of chemical modifications. The few specifically disclosed chemically modified siRNA molecules in Figures 4 and 5 contain chemical modification patterns that are very different from those recited in the claims. In addition, the application indicates that chemical modifications can be introduced at pyrimidine-containing nucleotides and further teaches that chemical modifications can be introduced "at the 3'-end, 5'-end, or both 3' and 5'-ends of the sense strand, antisense strand, or both strands."⁵ The Fosnaugh and Brown applications thus fail to teach or suggest first and second oligomeric compounds in which the first oligomeric compound comprises at least one 2'-fluoro modified nucleoside and the second oligomeric compound comprises an inosine base at the 3'-terminal hybridizing nucleoside.

Those of ordinary skill in the art therefore would have had *no reason* to produce oligomeric compounds containing the claimed pattern of chemical modifications at the time of the invention. Nothing in the Fosnaugh or Brown applications teaches or suggests the particular pattern of modifications claimed. One of skill in the art, having considered the Fosnaugh and Brown applications would have had no reason to expect that the particular combination of modifications claimed would confer any advantage to oligomeric compounds *relative to the advantageous properties said to be conferred by the thousands of other possible combinations of chemical modifications encompassed by the description provided in the Fosnaugh and Brown*

⁵ Paragraphs 18, 19, and 41.

applications. Accordingly, those of ordinary skill in the art thus would have had no reason to produce the claimed compounds.

Moreover, applicants have demonstrated that oligomeric compounds possessing the claimed pattern of chemical modifications inhibit target RNA expression.⁶ Since the Fosnaugh and Brown applications do not teach or suggest oligomeric compounds bearing the particular pattern of chemical modifications recited in the claims, the applications certainly cannot teach that such compounds would be effective at inhibiting target RNA expression. That is, nothing in the references teaches or suggests that the particular type, number, and pattern of chemical modifications recited in the present claims would result in oligomeric compounds that are effective to reduce target RNA expression *in vitro* by up to 66 %.⁷ The results described in Examples 3 and 4 of the present application would thus have been completely unexpected to those of ordinary skill in the art in view of the Fosnaugh and Brown applications.

The Fausnaugh and Brown applications fail to teach or suggest the claimed oligomeric compounds, and, moreover, there would have been no reason for those of ordinary skill in the art to design and produce oligomeric compounds possessing the particular pattern of chemical modifications recited in the claims at the time of the invention. The claimed oligomeric compounds therefore would not have been obvious to those of ordinary skill in the art, and applicants accordingly, respectfully, request withdrawal of the rejection.

B. Claims 1, 38, 40, and 58 have been rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by the Fosnaugh application in view of published U.S. patent application number 2005/0181382 ("the Zamore application"). Applicants respectfully request reconsideration and withdrawal of the rejection because the Fosnaugh and Zamore applications fail to teach or suggest the subject matter recited in the claims, and, hence, fail to render the claimed subject matter obvious.

As discussed above, the Fosnaugh application fails to teach or suggest first and second oligomeric compounds bearing the particular pattern of chemical modifications claimed.

⁶ Examples 3 and 4.

⁷ *Id.*

Instead, the Fosnaugh application merely provides generalized teachings regarding chemical modification of RNA. The Fosnaugh application provides a broad listing of possible chemical modifications for RNA and states that such modifications can be incorporated into siRNA molecules.⁸ The described chemical modifications could be incorporated into oligomeric compounds in a virtually limitless number of possible patterns and combinations. The Fosnaugh application does not provide any guidance or detail regarding the particular types of chemical modifications, the number of chemical modifications, and the positioning of chemical modifications that should be present in an siRNA molecule to impart beneficial properties to the molecule.

The Zamore application describes methods that are said to improve the efficiency of an RNAi reaction that involve modifying an siRNA duplex so that the base pair strength between the 5' end of the antisense strand and the 3' end of the sense strand is lessened relative to the base pair strength between the 5' end of the sense strand and the 3' end of the antisense strand.⁹ The application describes numerous and varied means for lessening the base pair strength between the 5' end of the antisense strand and the 3' end of the sense strand, including incorporating fewer G:C base pairs between the 5' end of the antisense strand and the 3' end of the sense strand than between the 3' end of the antisense strand and the 5' end of the sense strand; introducing a mismatched base pair, preferably a G:A, C:A, C:U, G:G, A:A, C:C, or U:U base pair, between the 5' end of the antisense strand and the 3' end of the sense strand; introducing a wobble base pair, such as a G:U base pair, between the 5' end of the antisense strand and the 3' end of the sense strand; introducing a rare nucleotide, such as inosine, 1-methyl inosine, pseudouridine, 5,6-dihydrouridine, ribothymidine, 2N-methylguanosine, or ^{2,2}N-dimethylguanosine, at the 5' end of the antisense strand or the 3' end of the sense strand; and introducing a base pair comprising a modified nucleotide, such as 2-amino-G, 2-amino-A, 2,6-diamino-G, or 2,6-diamino-A, between the 5' end of the antisense strand and the 3' end of the sense strand.¹⁰ The Zamore application does not teach that incorporating an inosine base into an

⁸ Paragraph 39.

⁹ Paragraph 37.

¹⁰ Paragraphs 43-47 and 59.

siRNA molecule would be any more advantageous or desirable than utilizing any of the other means described in the application to lessen base pair strength. Moreover, the Zamore application fails to describe or suggest compositions comprising two oligomeric compounds wherein one oligomeric compound comprises an inosine base and the other oligomeric compound comprises at least one 2'-fluoro modified nucleoside.

The appropriate design for chemically modified siRNA molecules having enhanced properties relative to unmodified compounds would have been unpredictable to those of ordinary skill in the art at the time of applicants' invention in view of the cited art. Such artisans would have had no reason to select the particular pattern of chemical modifications presently claimed from the enormous number of possible patterns of chemical modifications taught by the Fosnaugh and Zamore applications. The Fosnaugh and Zamore applications thus fail to teach or suggest first and second oligomeric compounds in which the first oligomeric compound comprises at least one 2'-fluoro modified nucleoside and the second oligomeric compound comprises an inosine base at the 3'-terminal hybridizing nucleoside.

Those of ordinary skill in the art therefore would have had *no reason* to produce oligomeric compounds containing the claimed pattern of chemical modifications at the time of the invention due to the fact that nothing in the Fosnaugh and Zamore applications teaches or suggests that the particular pattern of modifications claimed would confer any particular advantage to oligomeric compounds *relative to the advantageous properties said to be conferred by the thousands of other possible combinations of chemical modifications encompassed by the description provided in the Fosnaugh and Zamore applications*. Accordingly, those of ordinary skill in the art thus would have had no reason to produce the claimed compounds.

Moreover, applicants have demonstrated that oligomeric compounds possessing the claimed pattern of chemical modifications inhibit target RNA expression.¹¹ Since the Fosnaugh and Zamore applications do not teach or suggest oligomeric compounds bearing the particular pattern of chemical modifications recited in the claims, the applications certainly cannot teach that such compounds would be effective at inhibiting target RNA expression. That is, nothing in

¹¹ Examples 3 and 4.

the references teaches or suggests that the particular type, number, and pattern of chemical modifications recited in the present claims would result in oligomeric compounds that are effective to reduce target RNA expression *in vitro* by up to 66 %.¹² The results described in Examples 3 and 4 of the present application would thus have been completely unexpected to those of ordinary skill in the art in view of the Fosnaugh and Zamore applications.

The Fausnaugh and Zamore applications fail to teach or suggest the claimed oligomeric compounds, and, moreover, there would have been no reason for those of ordinary skill in the art to design and produce oligomeric compounds possessing the particular pattern of chemical modifications recited in the claims at the time of the invention. The claimed oligomeric compounds therefore would not have been obvious to those of ordinary skill in the art, and applicants accordingly, respectfully, request withdrawal of the rejection.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the official action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully submitted,

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/Jane E. Inglese/
Jane E. Inglese, Ph.D.
Registration No. 48,444

Woodcock Washburn LLP
Cira Centre
2929 Arch Street, 12th Floor
Philadelphia, PA 19104-2891
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

¹² *Id.*